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EXAMINER

POPA, ILEANA

ART UNIT

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1633

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DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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|------------------------------|--------------------------------------|--|--|
| Office Action Summary | Application No. 10/045,178 | Applicant(s) KASAHARA ET AL. | |
| | Examiner ILEANA POPA | Art Unit 1633 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 30 June 2010.
 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 41,43-46,49-51,56,58,59,61,63-73,75,78-82 and 87-121 is/are pending in the application.
 4a) Of the above claim(s) 46 is/are withdrawn from consideration.
 5) ☐ Claim(s) _____ is/are allowed.
 6) ☒ Claim(s) 41,43-45,49-51,56,58,59,61,63-73,75,78-82 and 87-121 is/are rejected.
 7) ☐ Claim(s) _____ is/are objected to.
 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.
 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
 Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413)
 Paper No(s)/Mail Date _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-40, 42, 47, 48, 52-55, 57, 60, 62, 74, 76, 77, and 83-86 have been cancelled. Claims 41, 80, 81, 87, 93, 97, 103, 195, 111, and 117-119 have been amended. Claim 46 has been withdrawn.

Claims 41, 43-45, 49-51, 56, 58, 59, 61, 63-73, 75, 78-82, and 87-121 are under examination.

Response to Arguments

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. (Cancer Research, 1993, 53: 83-88), in view of each Martuza et al. (U.S. Patent No. 5,585,096), Murakami et al. (Gene, 1997, 202: 23-29), and Sobol et al. (U.S. patent No. 5,674,486).

Ram et al. teach a method of treating glioblastoma (i.e., a cell proliferative disorder) in rats by the *in vivo* intratumoral administration of a therapeutically effective amount of cells producing a retrovirus comprising 5' and 3' long terminal repeats (LTR) and a heterologous nucleic acid sequence encoding the HSV thymidine kinase (tk) (i.e., a suicide gene) that uses the 5' LTR as its promoter (i.e., operably linked to a regulatory nucleic acid sequence), followed by contacting the rats with ganciclovir (i.e., a prodrug), wherein the ganciclovir is activated by the tk expression; since the cells are administered to the animal, they must necessarily be administered in a pharmaceutically acceptable carrier (i.e., the retrovirus is contained in a pharmaceutically acceptable carrier) (claims 41, 44, 45, 66, 78, 79, 87, 89, 97, 100, 105, 107, 119, and 121) (Abstract, p. 83, columns 1 and 2, p. 84, column 1, p. 85, column 2). Ram et al. teach that the retroviral vector is MoMLV, i.e., an MLV and a mammalian oncoretrovirus (claims 49, 61, 70, 80, 91, 99, 102, 109, and 115) (p. 83, column 1). Ram et al. teach their approach as suitable for the treatment of localized tumors in humans (Abstract, p. 83, column 2, second full paragraph, p. 88, column 1).

Ram et al. teach administering cells producing replication deficient MoMLV and not a replication competent retrovirus, as recited by the instant claims 41, 66, 80, 87, 89, 91, 97, 100, 102, 105, 107, 109, 119, and 121. However, at the time of filing, the advantages of using replication competent retroviruses for cancer treatment was taught by the prior art. For example, Martuza et al. teach that the administration of replication deficient viruses or of cells producing replication deficient viruses is not applicable to the treatment of tumors in humans because, since the virus cannot replicate, gene transfer

occurs within a few cell-distances, which leads to inefficient gene delivery; for these reasons, Martuza et al. suggest the use of replication competent viral vectors (including retroviral vectors) (column 2, lines 1-45, column 5, lines 14-18). Martuza et al. teach that such replication competent viruses can be used to treat melanoma (claims 56, 75, 98, and 101) (column 3, lines 52-55). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al. by using a replication competent MoMLV (i.e., an oncoretrovirus comprising MoMLV GAG, POL, ENV, and cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration into a target cell), with a reasonable expectation of success. The motivation to do so is provided by Martuza et al., who teach the necessity to replace replication deficient viruses with replication competent viruses for efficient gene therapy in animals and humans. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that replication competent viruses can be successfully obtained and used for cancer treatment. With respect to the limitation of the MoMLV being an amphotropic MoMLV (claims 50 and 71), since the teachings of Ram et al. and Martuza et al. (U.S. Patent No. 5,585,096) disclose MoMLV suitable for therapy in humans, their MoMLV must necessarily be amphotropic (i.e., allows transduction of cells of other species than the mouse).

Ram et al. and Martuza et al. do not teach a cassette comprising an internal ribosome entry site (IRES) operably linked to the suicide gene, wherein the cassette is located 5' to the 3' LTR and 3' to the sequence encoding ENV (claims 41, 66, 80, 87,

89, 91, 97, 100, 102, 105, 107, 109, 119, and 121). However, at the time of filing the use of cassettes comprising IRES operably linked to heterologous genes was known in the prior art, for example Murakami et al. teach insertions of such cassettes into retroviral vectors, wherein the cassettes are inserted 5' to the 3' LTR and 3' to the sequence encoding ENV (p. 25, Fig. 1A). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al. and Martuza et al. by inserting an IRES-suicide gene cassette in their MoMLV, as taught by Murakami et al., with a reasonable expectation of success. The motivation to do so is provided by Murakami et al. who teach that introduction of such IRES cassettes 5' to the 3' LTR and 3' to the sequence encoding ENV results in increased expression of heterologous genes as compared to the vectors lacking the IRES cassettes (Abstract, p. 23, column 2, last paragraph, p. 28, column 2, first full paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in doing so because Murakami et al. teach that IRES cassettes can be successfully inserted into retroviral vectors.

With respect to the limitation of a viral vector encoding a cytokine (claims 97, 100, 102, 105, 107, 109, and 119), Martuza et al. teach tumor killing by using replication competent viruses lacking a suicide gene and comprising a gene encoding a cytokine, wherein tumor killing is enhanced by cytokine expression in the tumor (column 11, lines 35-55). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made to substitute the suicide gene with a gene encoding a cytokine to achieve the predictable result of killing tumor cells. With respect to the limitations

recited in claims 116-118, it is noted that the art teaches cancer therapy by using a variety of cytokine, including IFN γ (see Sobol, Abstract, column 4, lines 25-27). It would have been obvious to one of skill in the art, at the time the invention was made to use a gene encoding IFN γ to achieve the predictable result of treating cancer.

With respect to the limitation of treatment by using a recombinant replication competent oncoretrovirus (instant claims 41, 80, 81, 87, 91, 93, 97, 102, 103, 105, 109, and 119), it is noted that the administration of the replication competent MoMLV to a patient would necessarily result in the *in vivo* production of the virus, and therefore, the combined teachings above embrace a method of treatment by using a recombinant replication competent MoMLV.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

5. Claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-121 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with each Martuza et al., Murakami et al., and Sobol et al., in further view of Douar et al. (Gene Ther, 1996, 3: 789-796, Abstract).

The teachings of Ram et al., Martuza et al., Murakami et al., and Sobol et al. are applied as above for claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121. Ram et al., Martuza et al., Murakami et al., and Sobol et al. do not teach a non-retroviral envelope, such as that of VSV (claims 119 and 120). Douar et al. teach VSV-G pseudotyped MoMLV (Abstract). It would have

been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al., Martuza et al., Murakami et al., and Sobol et al. by using a VSV-G pseudotyped MoMLV, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Douar et al. teach that VSV-G pseudotyped MoMLV has a broader host range. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the art teaches that VSV-G pseudotyped MoMLV can be successfully obtained and used. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

6. Claims 41, 43-45, 49-51, 56, 58, 59, 61, 66, 70, 71, 73, 75, 78-80, 87-92, 97-102, 105-110, 115-119, and 121 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with each Martuza et al., Murakami et al., and Sobol et al., in further view of both Vile et al. (Virology, 1995, 214: 307-313) and Yan et al. (Prostrate, 1997, 32: 129-139).

The teachings of Ram et al., Martuza et al., Murakami et al., and Sobol et al. are applied as above for claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121. Ram et al., Martuza et al., Murakami et al., and Sobol et al. do not teach an LTR comprising a tissue-specific promoter (claims 58, 88, 90, 92, 106, 108, and 110). Vile et al. teach a MoMLV vector wherein the LTR comprise the tissue specific tyrosinase promoter, wherein the tyrosinase promoter specifically targets viral gene expression in melanoma cells (Abstract, p. 308, column

1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the vector in the method of Ram et al., Martuza et al., Murakami et al., and Sobol et al. by introducing the tyrosinase promoter, within the LTR, with a reasonable expectation of success. One of skill in the art would have been motivated to use the tyrosinase promoter in order to target the expression of the suicide gene in melanoma cells. One of skill in the art would have been motivated to insert the tyrosinase promoter within the LTR because Vile et al. teach that inserting the tissue specific promoters within the LTR abolishes the promoter interference effects observed with retroviral vector wherein the tissue specific promoters are internally inserted (Abstract, p. 307, columns 1 and 2). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that promoters can be successfully introduced within the LTR.

Ram et al., Martuza et al., Murakami et al., Sobol et al., and Vile et al. do not teach the probasin promoter (claim 59). However, at the time of filing the probasin promoter was known and used in the prior art, for example the probasin promoter was used by Yan et al. to target gene expression in the prostate (Abstract, p. 130, columns 1 and 2, p. 133, column 2). Therefore, one of skill in the art would have known to use the probasin promoter to specifically target the suicide genes to prostate tumors for increased treatment efficiency of such tumors.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

7. Claims 41, 43-45, 49-51, 56, 58, 61, 63-73, 75, 78-82, 87-119, and 121 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ram et al. taken with each Martuza et al., Murakami et al., and Sobol et al., in further view of both Kasahara et al. (Science, 1994, 266: 1373-1376) and Vile et al.

The teachings of Ram et al., Martuza et al., Murakami et al., and Sobol et al. are applied as above for claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121. Ram et al., Martuza, Martuza et al., Murakami et al., and Sobol et al. do not teach a chimeric envelope, wherein the chimeric protein comprises a targeting ligand such as a receptor ligand (claims 63-65, 67-69, 73, 81, 82, 93, 95, 103, 104, 111, and 113) or an ecotropic envelope (claim 72). Kasahara et al. teach tissue specific targeting of MoMLV retroviral vectors to cells expressing the erythropoietin (EPO) receptor by engineering the vector to encode a chimeric ecotropic MoMLV protein, wherein the chimeric envelope protein comprises EPO (p. 1373, column 2, p. 1374, column 3 bridging p.1375). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ram et al., Martuza et al., Murakami et al., and Sobol et al. by engineering their vector to encode an ecotropic envelope fused to a receptor ligand, with a reasonable expectation of success. The motivation to do so is provided by Kasahara et al., who teach that such viruses can be used to specifically infect human cells expressing the receptor for the ligand and that such a strategy can be used for the treatment of cancer (p. 1373, column 1, p. 1375, column 1 bridging column 2, and column 3). One of skill in the art would have been expected to have a reasonable

expectation of success in doing such because the art teaches that such engineered retroviruses can be successfully made and used.

Ram et al., Martuza et al., Murakami et al., Sobol et al., and Kasahara et al. do not teach an LTR comprising a tissue-specific promoter (claims 58, 88, 90, 92, 94, 96, 106, 108, 110, 112, and 114). Vile et al. teach a MoMLV vector wherein the LTR comprise the tissue specific tyrosinase promoter, wherein the tyrosinase promoter specifically targets viral gene expression in melanoma cells (Abstract, p. 308, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the vector in the method of Ram et al., Martuza et al., Murakami et al., Sobol et al., and Kasahara et al., by introducing the tyrosinase promoter, within the LTR, with a reasonable expectation of success. One of skill in the art would have been motivated to use the tyrosinase promoter in order to target the expression of the suicide gene in melanoma cells. One of skill in the art would have been motivated to insert the tyrosinase promoter within the LTR because Vile et al. teach that inserting the tissue specific promoters within the LTR abolishes the promoter interference effects observed with retroviral vector wherein the tissue specific promoters are internally inserted (Abstract, p. 307, columns 1 and 2). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that promoters can be successfully introduced within the LTR.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant's arguments are not new and were previously addressed. The applicant argues again that Oh et al. (J Virol, 2002, 76: 1762-1768) demonstrate that even after the priority date of the present invention, those of skill in the art would not have been motivated to insert an IRES into mammalian retroviral systems. This argument is not found persuasive because the general and only teaching of "most retroviral genomes cannot accommodate the insertion of significant amounts of additional genetic information" in Oh et al. is not representative of what one of skill in the art would have known or have been motivated to do at the time the invention was made. In fact, Jespersen et al. (Gene, 1999, 239: 227-235) teach that foreign sequences (including IRES cassettes) can be successfully inserted into replication competent MLV to obtain stable expression vectors (Abstract; p. 228, paragraph bridging columns 1 and 2; p. 230, Fig.; p. 234, columns 1 and 2). Thus, before the teachings of Oh et al., the art demonstrates that: (i) replication competent MLV can successfully accommodate additional genetic information such as IRES cassettes; and (ii) based on the teachings of Murakami et al., one of skill in the art would have had a reasonable expectation of success in obtaining stable, replication competent MLV vectors by inserting IRES cassettes into replication competent MLV vectors.

Conclusion

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Jespersen et al. (Gene, 1999, 239: 227-235) was cited in response to applicant's argument that even after the priority date of the present

invention, those of skill in the art would not have been motivated to insert an IRES into mammalian retroviral systems. Specifically, the reference demonstrates that one of skill in the art would have reasonably expected to be successful in obtaining stable, replication competent MLV vectors by inserting IRES cassettes into replication competent MLV vectors.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633